Application Serial No. 10/420,310
Client/Matter No. 10546 - 109

REMARKS

Introductory Remarks:

Claims 1-32 are pending. Claims 1-17 and claim 32 are currently under examination. Claims 18-31 have been previously withdrawn. No new matter has been added.

In the Amendment and Response dated July 25, 2006, Applicant elected Group III, claims 2-13, and further elected viral vectors from Group III, with traverse of the restriction requirements of Groups I-V. With regard to the species election, applicant elected adenovirus. Applicant gratefully acknowledges that Examiner has found that the inventions of groups I-IV were related to the elected invention and therefore agreed to examine groups I-IV, claims 1-17 with the elected invention.

Claim Objections

Claims 4, 7 and 10 stand objected to as being dependent upon a rejected base claim and reciting non-elected subject matter. As discussed in Remarks below, Applicant disagrees with the Office's rejection of the base claims. Additionally, Applicant respectfully disagrees that the claims 4, 7 and 10 recite non-elected subject matter. Claim 4 claims an inducible promoter sequence. There was no requirement for or election among inducible promoter sequences. Claim 7 claims a vector with a nucleotide sequence of SEQ. ID. 5, which is a member of elected group III. Claim 10 claims complementary nucleotide sequence SEQ ID 6, which is a heat shock protein sequence. There has been no restriction or election involving heat shock protein sequences.

Claim Rejections – 35 U.S.C. § 103 (a)

Claims 1-3, 5-6, 11-13 and 32 stand rejected under 35 U.S.C. § 103(a) over Li et al. (US 2005/0032726), Frisan et al. (Int. J. Med. Microbiol. 2002), Sert et. al. (Oncogene 1999) and Xu et al. (Clinical Cancer Research 2001). Applicant respectfully

disagrees with these rejections because the Office has failed to establish a *prima facie* case of obvious for claims 1-3, 5-6, 11-13 and 32.

First, the § 103(a) rejections rely upon the Sert reference for teaching that CDTs, particularly *E. coli* CDT (which comprises *cdtA, cdtB and cdtC*) cause cell cycle arrest and DNA damage. The Sert reference teaches away from use of CDT's, particularly *E. coli* CDTs, for causing cell cycle arrest by DNA damage. Sert teaches that CDT triggers cell cycle arrest by a method that is independent of DNA damage (see page 6296, 6301). Sert further teaches that CDT does not induce double strand breaks (see page 6301). Sert teaches that CDT does not cause DNA damage through double strand breaks, which renders superfluous any motivation or desire to combine a CDT toxic gene with a second polynucleotide encoding an antisense oligonucleotide that inhibits expression of a DNA double strand break repair protein.

Second, the § 103(a) rejection also relies upon the Frisan reference for teaching that CDTs have the ability to induce cell cycle arrest or apoptosis in mammalian cells. Frisan teaches that *C. jejuni* cdtB has specific Dnase-I activity which induces DNA damage. However, Frisan does not teach that *cdtB*, used alone, is a good candidate as an anti-tumor agent. In fact, Frisan teaches away from using *cdtB* alone as an anti-tumor agent. Frisan teaches that expression of all three genes, *cdtA, cdtB and cdtC*, are required to produce an active CDT (see page 495). Frisan also states that all of the experimental preparations of cdtB contained cdtA and cdtC, leading the authors to suggest that ctdA and cdtC also play a role in the cell cycle arrest (see pages 495-496). Frisan does not teach or disclose any data that suggests CDTs are good anti-tumor agents. Rather, Frisan states that "[t]he interference of CDT with the cell cycle makes it a potentially good candidate for an anti-tumor agent" (see page 499). Because Frisan teaches that all three genes, *cdtA, cdtB and cdtC* are required to produce an active CDT and provides no evidence that cdtB alone causes DNA damage or cell cycle arrest, one would not have been motivated nor had a reasonable expectation of success for treating cancer with cdtB alone.

Third, the claimed invention solves a different problem from those solved by the cited Xu reference. The Xu reference is directed to solving the problem of insufficient drug concentration, systemic toxicity, lack of selectivity for tumor cells and drug resistant tumor cells through the use of exogenous enzymes delivered to tumor cells to selectively activate prodrug(s) delivered systemically (see page 3314). The Xu reference does not teach using a vector including one or more suicide genes and various control elements, and delivering the vector to a desired cell and placing the cell under conditions that induce the promoter.

Fourth, the Li reference discloses a method of increasing the sensitivity of cells to heat, chemical or radiation induced DNA damage (see [008]). The Li invention cannot be used alone as it does not induce DNA damage. The Li invention must be used in combination with other DNA damaging treatments to treat cancer. In contrast, the present invention can be used alone or in combination with other therapies as it combines a suicide gene which causes DNA damage through double strand breaks with an agent that inhibits repair of double strand breaks.

Fifth, the teachings of Sert, Frisan, Xu, and Li, alone or in combination, do not supply all of the elements of the present invention. The instant claims are drawn to a gene therapy vector comprising a first polynucleotide encoding a gene for B subunit of a cytolethal distending toxin; and a second polynucleotide encoding an antisense oligonucleotide that inhibits expression of a sense oligonucleotide encoding a DNA repair protein; wherein the first and second polynucleotides are operably linked to an inducible promoter.

Sert teaches that CDT does not cause DNA damage therefore teaches away from using CDT in combination with disruption of a DNA repair protein. Frisan teaches that use of the CDT (comprising the A, B, and C subunits), is necessary to cause cell cycle arrest and thus teaches away of the use of only the B subunit. Li et al teaches an expression vector comprising a heat shock promoter operably linked to an antisense compound targeted to a gene encoding a DNA repair protein to increase the sensitivity of cancer cells to heat, chemical or radiation-induced DNA damage. Li does not teach a

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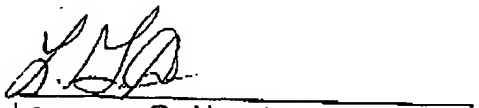
gene therapy vector comprising a B subunit of a CDT. In light of the teaching away of Sert and Frisan, there would be no motivation to combine the gene therapy vector in Li with a B subunit of a CDT. Finally, Xu teaches strategies for cancer therapy comprising administering non-toxic activating enzymes to cancer cells wherein the non-toxic enzyme activates a systematically administered pro-drug causing the systematically administered pro-drug to cause cancer cell death. Xu does not teach or suggest strategies or vectors for cytotoxic gene therapy consisting of a DNA damaging toxin operably linked to a antisense oligonucleotide which inhibits expression of DNA repair proteins.

For at least these reasons the Office has failed to establish a *prima facie* case of obviousness of claims 1-3, 5-6, 11-13 and 32.

SUMMARY

The claims at issue are distinguished over the cited references and are in condition for allowance. Accordingly, such allowance is now earnestly requested The Examiner is invited to contact the undersigned attorneys for the Applicant via telephone if such communication would expedite this application.

Respectfully submitted,



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